accompanied by a package insert meeting the requirements of §809.10 of this chapter. If two or more final containers requiring identical package inserts are placed in a single package, only one package insert per package is required.

(d) *Names of antibodies.*

Antibody designation on container label	Definition
(1) Anti-IgG, -C3d; Polyspecific.	Contains anti-IgG and anti-C3d (may contain other anticomplement and anti-immunoglobulin antibodies).
(2) Anti-IgG	Contains anti-IgG with no anti-complement activity (not necessarily gamma chain specific).
(3) Anti-IgG; heavy chains.	Contains only antibodies reactive against human gamma chains.
(4) Anti-C3b	Contains only C3b antibodies with no anti-immunoglobulin activity. **Note:** The antibody produced in response to immunization is usually directed against the antigenic determinant which is located in the C3c subunit; some persons have called this antibody "anti-C3c." In product labeling, this antibody should be designated anti-C3b.
(5) Anti-C3d	Contains only C3d antibodies with no anti-immunoglobulin activity.
(6) Anti-C4b	Contains only C4b antibodies with no anti-immunoglobulin activity.
(7) Anti-C4d	Contains only C4d antibodies with no anti-immunoglobulin activity.

Anti-Human Globulin preparations may contain one or more of the antibody specificities listed in this paragraph as described in paragraph (a)(2)(i) of this section.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985; 50 FR 9800, Mar. 12, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 55 FR 11014, Mar. 26, 1990]

Subparts G–J—[Reserved]

Subpart K—Limulus Amebocyte Lysate

§ 660.100 Limulus Amebocyte Lysate.

The proper name of this product shall be Limulus Amebocyte Lysate. The product is defined as an extract that is derived from the blood of *Limulus polyphemus* and is capable of detecting bacterial endotoxins.

[45 FR 32299, May 16, 1980]

§ 660.101 U.S. Standard/Reference Preparations.

The following U.S. Standard/Reference preparations shall be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, for use as prescribed in this subpart:

(a) A U.S. Standard Endotoxin for determining the sensitivity of Limulus Amebocyte Lysate.

(b) A U.S. Reference Limulus Amebocyte Lysate for establishing the potency of Limulus Amebocyte Lysate.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 660.102 Potency test.

A sample of each final filling of each lot of Limulus Amebocyte Lysate and the U.S. Reference Lysate shall be tested in parallel with the U.S. Standard Endotoxin. If the product is freeze-dried after filling, the test shall be conducted on samples from each filling in each drying chamber run. The procedure for rehydrating and mixing the lysate for the potency test shall be that specified in the manufacturer's package insert. A minimum of 8 vials and a maximum of 28 vials from each filling or, if freeze-dried, from each drying chamber run representing all parts of the chamber load, shall be tested in parallel with an equal number of tests from 1 or more vials of the U.S. Reference Lysate. The test shall be performed as follows:

(a) *Dilution of U.S. Standard Endotoxin.* A single series of consecutive two-fold dilutions, beginning with a concentration of the U.S. Standard Endotoxin at least four-fold above the endpoint, shall be prepared with a range selected to bracket the endpoint for both the U.S. Reference Lysate and test lysate filling in each test performed.

(b) *Test procedure.* (1) Transfer 0.1 milliliter of each concentration of U.S. Standard Endotoxin, as prepared in paragraph (a) of this section, into each of two test tubes having an inside diameter not greater than 10 millimeters, unless the use of another size test

tube has been approved by the Director, Center for Biologics Evaluation and Research.

(2) Add 0.1 milliliter of the U.S. Reference Lysate to one of the tubes containing the lowest concentration of U.S. Standard Endotoxin. Add 0.1 milliliter of test lysate to the second tube containing the lowest concentration of U.S. Standard Endotoxin.

(3) Repeat the procedure in paragraphs (b)(1) and (2) of this section for each dilution of the U.S. Standard Endotoxin and for each vial of lysate to be tested from each filling of the test lot, progressing from the lowest endotoxin concentration to the highest.

(4) Immediately following addition of the lysate to each tube, mix the contents gently and place in a 37° C water bath for 1 hour.

(c) *Validity of the test.* (1) Record the reaction in each tube as either positive or negative. A positive reaction is demonstrated by a firm gel that remains intact, at least momentarily, when the tube is inverted 180 degrees. For Limulus Amebocyte Lysate that does not require gelation as an indicator of reactions, the endpoint shall be determined by the method specified in the labeling for the product.

(2) For each parallel test obtain the ratio of endpoints of reference and test lysates. Calculate the standard deviations (S.D.) of log ratios.

(3) The test is valid if the S.D. is less than or equal to the value for the 99 percent fiducial upper limit of the S.D. of the sample size tested. The S.D. table is shown in paragraph (d) of this section.

(4) If the S.D. is greater than the tabulated value, the test may be expanded up to the maximum of 28 parallel tests and a new S.D. for log ratios may be calculated.

(5) The tests are invalid due to excessive variability if the S.D. is greater than the value in the S.D. table corresponding to the sample size tested.

(6) If the S.D. is within the limits, the geometric mean (G.M.) of the ratios shall be calculated.

(7) The endpoints of U.S. Reference and test lysates, ratios of endpoints, S.D. of log ratios, and G.M. of ratios shall be calculated and reported on the protocol submitted to the Director, Center for Biologics Evaluation and Research.

(d) *S.D. table.* Ninety-nine percent fiducial upper limit on S.D. of $\log_2$ (ratio):

Sample size	Upper limit
4	[1] 1.02
8	0.86
12	0.79
16	0.75
20	0.73
24	0.71
28	0.69

[1] Limits can be converted to $\log_{10}$ by multiplying each value by 0.3.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 52 FR 39637, Oct. 23, 1987; 55 FR 11013, Mar. 26, 1990]

§ 660.103 General requirements.

(a) *Handling the horseshoe crabs.* The horseshoe crabs (*Limulus polyphemus*), from which blood is collected for production of the lysate, shall be handled in a manner so as to minimize injury to each crab. The horseshoe crabs shall be returned alive to their natural environment after a single collection of their blood.

(b) *Processing.* The processing methods shall be those which have been shown to yield consistently a potent and detection-specific final product free of properties that would adversely affect the accuracy of the test results when the Limulus Amebocyte Lysate is used by the methods recommended by the manufacturer in the package insert.

(c) *Final containers.* Final containers at the time of filling shall be sterile, nonpyrogenic, colorless, and transparent.

(d) *Date of manufacture.* The date of manufacture of each filling of each lot shall be the date the manufacturer initiated the last valid potency test for such filling. The results from this test shall be reported on the protocol submitted to the Director, Center for Biologics Evaluation and Research.

(e) *Sterility test.* A sterility test shall be performed on the bulk lot and on each filling as prescribed in §610.12 of this chapter.

(f) *Test for quality.* A test for lysate quality shall be performed as follows: